REMARKS

This amendment responds to the office action mailed January 28, 2003. Claims 1-37 were pending in the instant Application. With the instant amendment, claims 34-37 have been canceled without prejudice, as drawn to non-elected subject matter. Claims 1-33 have been canceled, without prejudice, and replaced by new claims 38-88. Thus, after entry of the instant amendment, claims 38-88 are pending and under consideration.

New claims 38-88 are fully supported by the specification and the claims as originally filed. Support for new claims 38-40 can be found in, for example, claim 1, as originally filed, as well as in the specification, at, for example, pages 12 or 39. Support for new claims 41-43 can be found in, for example, claims 2-4, respectively, as originally filed. Support for new claims 44 and 45 can be found in, the specification at, for example, pages 20 and 40-41. Support for new claim 46 and 47 can be found in, for example, claims 5 and 6, respectively, as originally filed. Support for new claim 48 can be found in, for example, claim 7, as originally filed, as well as in the specification, at, for example, page 13. Support for new claims 49 and 50 can be found in, the specification in, for example, Example 1, in particular, at pages 46-48. Support for new claims 51-52 can be found in, for example, claims 9-10, respectively, as originally filed. Support for new claims 53-54 can be found in, for example, claim 11, as originally filed. Support for new claims 55-71 can be found in, for example, claims 12-28, respectively, as originally filed. Support for new claims 72 and 73 can be found in, for example, claims 31 and 33, respectively, as originally filed. Support for new claims 74 and 75 can be found in, for example, claim 33, as originally filed, and in the specification, at, for example, page 16. Support for new claims 76-78 can be found in, for example, claim 33, as originally filed, and in the specification, at, for example, pages 12-13 and 16. Support for new claims 79 and 80 can be found in, for example, claim 33, as originally filed, and in the specification, at, for example, page 16 and in Example 1 or Example 8. Support for new claims 81-83 can be found in, for example, claim 33, as originally filed, and in the specification, in, for example, Example 8. Support for new claims 84-88 can be found in, for example, claim 33, as originally filed, and in the specification, at, for example, pages 12-13 and 16 and in Example 8.

Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

It has been noted that a new oath or declaration is required. A declaration executed by three of the four inventors is filed herewith. The fourth inventor, however, was not available at this time. Applicants respectfully submit that they will file a fully executed declaration in accordance 37 CFR 1.67(a) as soon as the fourth inventor is available.

I. THE REJECTIONS UNDER 35 U.S.C. §112, FIRST AND SECOND PARAGRAPHS SHOULD BE WITHDRAWN

Claims 29 and 30 stand rejected under 35 U.S.C. § 112, first and second paragraphs. Applicants respectfully submit that cancellation of claims 29 and 30 obviates these rejections. As such, Applicants respectfully request that these rejections be withdrawn.

II. THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 1-28 and 31-33 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Gao *et al.*, 1996, *Journal of Virology*, **70**:1651-1667 ("Gao") and Petropoulos *et al.*, 2000, *Antimicrob. Agents. Chemother.*, **44**:920-928 ("Petropoulos") in view of Grovit-Ferbas *et al.*, 1998, *Journal of Virology*, **72**:8650-8658 ("Grovit") and Trkola *et al.*, 1999, *Journal of Virology*, **73**:8966-8974 ("Trkola"). As pointed out, above, none of claims 1-28 and 31-33 are currently pending. However, for the reasons set forth below, Applicants assert that the pending claims are not rendered obvious in view of Gao and Petropoulos in view of Grovit and Trkola.

A. The Legal Standard

To reject a claim as under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the PTO must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination rests or relies on the combination of two or more references, there must be some suggestion or motivation to

combine the references. *See WMS Gaming Inc. v. International Game Technology,* 51 U.S.P.Q.2d 1386 (Fed.Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

However, the mere fact that the prior art could be modified to produce the claimed invention does not make the modification obvious unless the prior art also suggests the desirability of the modification. *See In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). Rigorous application of the requirement for a showing of such motivation to combine references is the best defense against the subtle but powerful attraction of an impermissible hindsight-based obviousness analysis. *See In re Dembiczak*, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor 's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight." *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside,* 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a *prima facie* case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

B. The PTO has Failed to Establish *Prima Facie* Obviousness Against any of the Pending Claims

Claims 1-28 and 31-33 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Gao and Petropoulos in view of Grovit and Trkola. As pointed out, above, none of claims 1-28 and 31-33 are currently pending. However, for the reasons set forth below, Applicants assert that none of the pending claims are rendered obvious in view of the cited references.

Applicants respectfully submit that the references cited by the PTO first, are not sufficient to establish a *prima facie* case of obviousness against the pending claims, because none of Gao, Petropoulos, Grovit or Trkola, alone or in any combination, teaches or suggests

each and every element of the pending claims. As discussed above, in order to establish *prima facie* obviousness, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. By failing to make such a showing, the PTO has failed to establish *prima facie* obviousness against the pending claims.

Nowhere in Gao are the methods of the pending claims taught, nor do any teachings of Gao suggest a method for identifying whether a compound inhibits entry of a virus into a cell. Gao reports the generation of a panel of genetically diverse, functionally active *env* genes from various parts of the world (see, abstract, and p. 1652, right column). The purpose of study presented in Gao is to begin use the genetically diverse *env* sequences to understand structure, function and immunogenicity of naturally occurring envelope glycoproteins of HIV (see abstract).

Gao postulates that the panel will also contribute to AIDS vaccine development efforts. In particular, Gao states that the diverse functional sequences may be useful in identifying particular antigens that could be tested in subunit vaccines (p. 1665, left column). Alternatively, Gao postulates that the functional sequences could contribute to determining whether a phenomena referred to in Gao as "fusion enhancement" may represent an obstacle to vaccine development. (*Id.*)

Gao therefore, is only concerned with identification of structurally diverse, but functional, *env* sequences. Nowhere does Gao teach or suggest use of the *env* sequences in conjunction with, or to identify drugs or compounds that inhibit viral entry. In fact, the PTO itself acknowledges that Gao does not teach or suggest an assay to determine the ability of a compound to inhibit viral entry into a permissive cell (Office Action, bottom of p. 9).

Petropoulos does not remedy the deficiencies of Gao. Petropoulos does not teach or suggest each and every element of the methods of the pending claims. Petropoulos teaches susceptibility and resistance assays to protease inhibitors and reverse transcriptase inhibitors using resistance test vectors that contain a luciferase gene and protease and reverse transcriptase sequences derived from HIV-1-infected patients (Petropoulos, Abstract). Petropoulos does not teach or suggest a viral particle comprising a nucleic acid encoding a viral envelope protein obtained from a patient infected by the virus. In fact, the resistance test vector of Petropoulos is specifically designed to *not* include a HIV-*env* sequence. In particular, a luciferase expression cassette is inserted within a *deleted* region of the HIV-1

env gene (Petropoulos, p. 921, left column, figure legend, p. 922). Further, the PTO also acknowledges that Petropoulos does not teach a method for assaying "for compounds that may inhibit viral entry" into a cell (Office Action, middle of p. 10).

Grovit does not remedy the deficiencies of Gao or Petropoulos. Grovit does not teach or suggest each and every element of the methods of the pending claims. Like Gao, Grovit attempts to study structure-function relationships of various *env* sequences, but focuses on *env* sequences from long-term survivors of HIV-1 (Grovit, p. 8650, right column). Like Gao, Grovit also fails to teach or suggest use of *env* sequences in conjunction with, or to identify, drugs or compounds that inhibit viral entry. In fact, as acknowledged by the PTO, Grovit "does not teach assaying compounds for their ability to interfere with viral entry" (Office Action, middle of p. 10).

Similarly, Trkola does not remedy the deficiencies of Gao or Petropoulos. Trkola does not teach or suggest each and every element of the methods of the pending claims. Instead, Trkola merely teaches creation of a cell line that can be infected by phenotypically diverse HIV isolates. The cell line-based assay is reported to be no more or less sensitive than PBMC-based assays (Trkola, p. 8972, right column). Trkola is certainly not the first reference to mention the possibility of developing an AIDS vaccine, nor, are antibodies even a primary focus of Trkola. Rather than teaching the use of antibodies as a compound for inhibiting viral entry into a cell (as the PTO concludes; Office Action, p. 11), Trkola only concludes that previous failures of gp120 subunit vaccines to generate neutralizing antibodies appear to be more dependent on virus-antibody interaction rather than virus-cell interactions, *i.e.*, the previous failures were most likely not due to use of PBMC-based assays. Trkola does not teach or suggest use of *env* sequences in conjunction with its cell line at all, let alone in conjunction with, or to identify a compound that inhibits viral entry.

The PTO acknowledges that *none* of the references teach or suggest a method of assaying a compound for its ability to inhibit viral entry into a cell. Yet, the PTO alleges that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to test a patient derived HIV sample for the ability to be inhibited by a compound that will prevent viral entry " (Office Action, 2nd paragraph of p. 11). Applicants respectfully remind the PTO that in order to establish a *prima facie* case of obviousness, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside,* 53 U.S.P.Q.2d 1769.

As summarized above, Gao and Grovit are concerned with structural and functional features of *env* sequences, while Petropoulos is directed to assessing the susceptibility of HIV to protease and reverse transcriptase inhibitors, and Trkola merely teaches cells lines that can be infected with diverse HIV sequences. Nothing in these references teaches or suggests reworking and reengineering the Petropoulos assay to attempt to assess *env* sequences' susceptibility to entry inhibiting drugs. As such, the PTO has failed to make the requisite showing that the combination of Gao, Petropoulos, Grovit and Trkola teaches or suggests each and every element of the pending claims.

The Federal Circuit has indicated that a *prima facie* case of obviousness requires "objective evidence of record" demonstrating that there is prior art that teaches or suggests combining the asserted references as proposed. *In re Lee*, 277 F.3d 1338, 1341 (Fed. Cir. 2002). The Court has also made clear that the requirement for a showing of the teaching or motivation to combine prior art references must be "clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence." *In re Dembiczak*, 173 F.3d 994, 999 (Fed. Cir. 1999). As discussed below, the PTO has also failed to demonstrate this second prong required for a *prima facie* obviousness rejection.

The PTO utilizes Gao and Petropoulos as primary references. In particular, the PTO utilizes Gao to contend that it would have been obvious to utilize a patient-derived *env* segment to test drug susceptibility. The PTO utilizes Petropoulos to contend that drug susceptibility assays have been used for determining susceptibility to protease inhibitors and reverse transcriptase inhibitors. However, as discussed above, the purpose of the Gao study was to use a single-round virus infectivity assay to understand structure, function and immunogenicity of genetically diverse *env* sequences and envelope glycoproteins of HIV.

Thus, the goal of Gao was directed to identifying *common* structure and functional characteristics present amongst widely diverse populations of HIV, for example, to identify antigens *conserved* amongst as wide a population of HIV clades as possible. In complete contrast, the goal of Petropoulos was to assess the *unique* responses of a *particular* patient's HIV to a given drug. Clearly, therefore, one of ordinary skill in the art would have had no motivation or reason to combine the teachings of Gao and Petropoulos.

Grovit adds nothing more than Gao in that Grovit is also directed to identifying functional characteristics of *env* sequences, in this case in *env* sequences present in long term HIV-1 survivors. Moreover, it is noted that while Grovit states that its data supports a

hypothesis that viral entry may be a determinant of long-term survival, Grovit also acknowledges that "other viral genes may be involved in the growth attenuation phenotype" of the virus from the long-term survivor (p. 8656, left column).

Trikola also fails to provide motivation to combine the cited references. As discussed above, Trikola merely describes a cell line that works in a manner no more or less effectively than standard PBMC-based assays.

Merely alleging that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to test a patient derived HIV sample for the ability to be inhibited by a compound that will prevent viral entry" (Office Action, p. 11) cannot sufficient to demonstrate a motivation to combine these references in a manner that would yield the claimed invention. *See In re Dembiczak*, 173 F.3d at 999.

Finally, as discussed below, even assuming *arguendo,* that the combination of four references cited by the PTO does indeed suggest the claimed invention, which it does not, these references alone or in combination, fail to provide a reasonable expectation of success for the claimed invention. Thus, the PTO has also failed to demonstrate the third prong required for a *prima facie* obviousness rejection.

Petropoulos teaches particular vectors that are used to assess an HIV-1-infected patient's susceptibility to protease inhibitors and reverse transcriptase inhibitors. The Petropoulos reference teaches nothing about attempting to utilize such vectors to assess the susceptibility of a patient's HIV to drugs directed at any other HIV target. With respect to *env* targets in particular, it is further noted that the vector described in Petropoulos was, in fact, designed to *lack* an HIV *env* sequence (Petropoulos, p. 921, left column, figure legend, p. 922). Even assuming, *arguendo*, that the combination of Petropoulose and Gao, together with Grovit and Trkola, did suggest testing a patient-derived *env* sequence for the ability to be inhibited by a compound that will inhibit viral entry, the fact that Petropoulos shows that this is possible for different HIV targets (protease and reverse transcriptase) provides no indication as to whether an assay involving a completely different target (*env*) would work, and would surely fail to provide one of ordinary skill in the art with the necessary *reasonable expectation* that such an *env* assay would succeed.

In conclusion, Applicants respectfully submit that the PTO has failed to satisfy all three prongs of the three-part test to render a claimed invention *prima facie* obvious. First, the PTO has not satisfied its burden of showing that the prior art references, either alone or in

combination, teach or suggest each and every limitation of the rejected claims. Next, the PTO has failed to show any suggestion or motivation to combine the references. Finally, the prior art references cited by the PTO fail to suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success.

Accordingly, Applicants submit that the pending claims are not rendered obvious by Gao, Petropoulos, Grovit or Trkola, alone or in any combination.

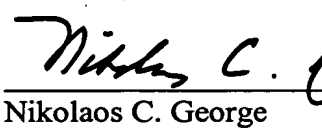
CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that claims 38-88 satisfy all the criteria for patentability and are in condition for allowance. Applicants request that the Examiner reconsider this application with a view towards allowance and solicit an early passage of claims 38-88 to issuance. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Pursuant to 37 CFR § 1.136(a)(3), the Commissioner is hereby authorized to charge all required fees, including fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP U.S. Deposit Account No. 16-1150 (order no. 11068-052-999).

Respectfully submitted,

Date: July 28, 2003



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